THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Neuromusculoskeletal interfacing of lower limb prostheses

ALEXANDER THESLEFF

Department of Electrical Engineering

CHALMERS UNIVERSITY OF TECHNOLOGY

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Department of Electrical Engineering,
Division of Systems and Control
Chalmers University of Technology
SE-412 96 Gothenburg
Sweden
Telephone + 46 (0)31-772 1000

Cover:
The illustration on the front cover is an illustration of the neuromusculoskeletal interface known as the e-OPRA Implant System used to attach a lower limb prosthesis to the residual limb. The illustration has been created by Sara Manca.

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Neuromusculoskeletal Interfacing of Lower Limb Prostheses

ALEXANDER THESLEFF
Department of Electrical Engineering,
Division of Systems and Control
Chalmers University of Technology

Abstract

The method of bone-anchored attachment of limb prostheses via a percutaneous skeletal extension was developed to circumvent commonly reported problems associated with the conventional method of socket attachment. In addition to the direct structural connection, the percutaneous implant may serve as a conduit for bidirectional communication between muscles and nerves within the residual limb and the prosthesis. Implanted electrodes recording myoelectric activity within the residual limb can be used to infer the user's movement intent and may thus be used to provide intuitive control of the prosthesis in real time. Sensory feedback from the prosthesis can be provided back to the user by neurostimulation via implanted neural electrodes, thus closing the control loop. Together the skeletal, neural, and muscular interfaces form a neuromusculoskeletal interface. This technology is currently being evaluated in a clinical trial on individuals with upper limb amputation, but it has not yet been used in the lower limb.

The aim of this thesis has been to translate the concept of neuromusculoskeletal interfacing to the lower limb. An additional aim has been to reduce the limitations on high impact activities, that exist on current available systems for bone-anchored attachment of limb prostheses. To achieve these aims, a new design of the neuromusculoskeletal interface was developed where the structural capacity was increased with respect to current versions of the implant system to accommodate increased loads for highly active usage by individuals with lower limb amputation. In order to set adequate design requirements, investigations were conducted to determine the load exposure of bone-anchored implant systems during a number of loadbearing activities. Structural verification of the neuromusculoskeletal interface has been performed using numerical simulations as well as physical testing in static and dynamic conditions. The first steps towards clinical implementation of the lower limb neuromusculoskeletal interface have been taken by the development of a clinical research protocol that has been approved by the Swedish Ethical Review Authority.

Keywords: Osseointegration; neuromusculoskeletal interface, bone-anchored attachment, direct skeletal attachment, Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA), OPRA; Enhanced Osseointegrated Prostheses for the Rehabilitation of Amputees (e-OPRA).

Preface

This thesis is in fulfillment for the degree of Doctor of Philosophy (PhD) at Chalmers University of Technology. The thesis has been carried out in a collaboration between Chalmers University of Technology, Sahlgrenska University Hospital, and the industrial partner Integrum AB. The author was employed by the latter as part of an Industrial PhD grant by the Swedish Foundation for Strategic Research (SSF).

The work resulting in this thesis was carried out between August 2016 and May 2021 at the Center for Bionics and Pain Research (CBPR) and within the Bionics Unit at the Division of Systems and Control at the Department of Electrical Engineering at Chalmers University of Technology, and at Integrum AB, Mölndal.

Associate Professor Max Ortiz Catalan was the main supervisor and Professor Bo Håkansson was co-supervisor for the thesis. M.D. PhD. Rickard Brånemark acted as the industry supervisor. The work has been financially supported by SSF, the Swedish Innovation Agency (VINNOVA), the Promobilia Foundation, the IngaBritt and Arne Lundbergs Foundation, and Integrum AB.

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Finally, I want to thank my wife, Emma. You are the most important person in my life. I want to thank you for your unconditional support day after day. Thank you for bringing me so much joy and happiness.

List of Publications

The thesis is based on the work contained in the following papers, referred to by Roman numerals in the text:

I Thesleff, A., Brånemark, R., Håkansson, B., Ortiz-Catalan, M. “Biomechanical Characterisation of Bone-anchored Implant Systems for Amputation Limb Prostheses: A Systematic Review”. Ann Biomed Eng 46, 377–391 (2018). https://doi.org/10.1007/s10439-017-1976-4

II Thesleff, A., Häggström, E., Tranberg, R., Zügner, R., Palmquist, A., Ortiz-Catalan, M. "Loads at the Implant-Prosthesis Interface During Free and Aided Ambulation in Osseointegrated Transfemoral Prostheses", in IEEE Transactions on Medical Robotics and Bionics, vol. 2, no. 3, pp. 497-505, Aug. 2020, doi: 10.1109/TMRB.2020.3002259.

III Thesleff A., Ludvigsson S., Öhr E., Ortiz-Catalan M. “Load exposure of osseointegrated implants for transfemoral limb prosthesis during running”. Annu Int Conf IEEE Eng Med Biol Soc. 2018 Jul;2018:1743-1746. doi: 10.1109/EMBC.2018.8512592. PMID: 30440732.

IV Thesleff, A., Ortiz-Catalan, M., Brånemark, R., “The effect of cortical thickness and thread profile dimensions on stress and strain in bone-anchored implants for amputation prostheses”, Manuscript submitted, Preprint doi: 10.36227/techrxiv.14499759

V Thesleff, A., Ortiz-Catalan, M., Brånemark, R., “Low plasticity burnishing improves fretting fatigue resistance in bone-anchored implants for amputation prostheses”, Manuscript submitted, Preprint doi: 10.36227/techrxiv.14502450

VI Thesleff, A., Ahkami, B., Anderson, J., Hagberg, K., Ortiz-Catalan, M. “Design of a stepwise safety protocol for lower limb prosthetic risk management in a clinical investigation”, Manuscript submitted, Preprint doi: 10.36227/techrxiv.14501493

Acronyms

OPRA	Osseointegrated Prostheses for the Rehabilitation of Amputees
EMG	Electromyography
MPK	Microprocessor controlled prosthetic knee
SACH	Solid ankle cushion heel
ESAR	Energy storage and return
MPF	Microprocessor controlled prosthetic foot
PMA	Premarket Approval
FDA	Food and Drug Administration
ILP	Integral Leg Prosthesis
EEP	Endo-Exo Prosthesis
OPL	Osseointegrated Prosthetic Limb
OFP	Osseointegrated Femur Prosthesis
OTP	Osseointegrated Tibia Prosthesis
ITAP	Intraosseous Transcutaneous Amputation Prosthesis
KWA	Keep Walking Advanced
POP	Percutaneous Osseointegrated Prosthesis
TMR	Targeted muscle reinnervation
RPNI	Regenerative peripheral nerve interface
AMI	Agonist-antagonist myoneural interface
CAD	Computer Aided Design
FEA	Finite Element Analysis
LPB	Low plasticity burnishing
SEM	Scanning electron microscopy

Contents

1. Introduction

In order to describe the scope of this thesis, some introductory information is first given in this chapter.

1.1. Conventional suspension of prosthetic limbs

The conventional method for attachment of a limb prosthesis to the body is via a socket which compresses the soft tissues of the residual limb. However, the socket connection is the source of many of the commonly reported problems for prosthesis users, such as discomfort, skin problems, perspiration and poor fit [1]–[6]. A reason for this is the high compressive and frictional forces required for adequate retention of the prosthesis and the difficulty to achieve a good fit between the socket and the residual limb. These problems may limit the prosthesis usage, reduce the ability to ambulate with the prosthesis, and lead to reduced participation in social activities [3], [4], [6], [7]. For individuals with a short residual limb, skin disorders, heterotopic ossification, or other conditions which affect the residual limb, a socket may not be a viable option. These individuals may be relegated to a wheelchair and/or abandon their artificial limb. It was to address these issues that the concept of bone-anchored attachment of limb prostheses was developed.

1.2. Bone-anchored attachment of prosthetic limbs and the OPRA Implant System

Bone-anchoring of prostheses is a concept in which a percutaneous skeletal extension of the residual bone is created, allowing for attachment of a prosthesis without a socket. The method builds on the discovery that bone tissue may form an exceptionally intimate and mechanically stable connection with titanium [8]. This phenomenon is now known as osseointegration and is defined as “the firm anchoring of a surgical implant by the growth of bone around it without fibrous tissue formation at the interface” [9]. The first clinical applications of osseointegration were in dental field, but it has since then spread to other applications such as hearing aids, facial reconstructions and orthopedic applications including bone-anchored attachment of prosthetic limbs [10]. The method was developed in Sweden and the Swedish system for bone-anchored attachment of prosthetic limbs, known as the OPRA (Osseointegrated Prostheses for the Rehabilitation of Amputees) Implant System (Integrum AB, Mölndal) is a market leader for this application.

1.3. e-OPRA Implant System

Beyond the attachment of the prosthesis to the skeleton, bone-anchored attachment also opens up for further integration between the prosthesis and the human body. A recent enhancement of the OPRA Implant System for upper limb users has led to a neuromusculoskeletal interface known as the e-OPRA Implant System, where in addition to the skeletal attachment, a direct connection with muscles and nerves within the residual limb is also achieved via implanted electrodes [11], [12]. This allows for the recording of electromyographic (EMG) signals from the muscles in the residual limb. With the recorded signals the prosthesis can be volitionally controlled by the user [13]–[15]. Furthermore, sensors on the prosthesis are in direct contact with the implanted electrodes which allows for sensory feedback via neurostimulation in

response to external stimuli of the prosthesis [16]. This means that the user can perceive sensations with their prosthesis in the same way as with an intact limb. The proven success of the e-OPRA Implant System in the upper limb [12] may be attainable also for the lower limb. If realized, this has the potential to substantially push the frontier of prosthetic control of lower limb prostheses, as it would provide the first permanent, stable neuromusculoskeletal interface in individuals with lower limb amputation. With this interface, one of the largest barriers preventing neural control of lower limb prostheses from becoming clinically feasible would be removed.

1.4. Need for further development

The current version of the OPRA Implant System for the lower limb is designed for, and functions well in activities of everyday living, but for safety reasons, there are restrictions on high impact activities. For example, it is advised against running and jumping with the prosthesis attached to the implant. Additionally, the highest body weight acceptable for treatment with the OPRA Implant System is 100 kg. For conservative reasons, the treatment has primarily been recommended for individuals who have or are expected to have problems with a conventional socket attachment. Since there are not many individuals with a transfemoral amputation who would be able to run with a standard prosthesis in the first place, the activity limitations are not very restrictive. However, it has been shown that bone-anchored attachment of limb prostheses often leads to increased mobility and prosthesis usage [17]–[19] and with this increased capability comes a desire to perform more demanding activities. Furthermore, if current indications for use of the OPRA Implant System were to be updated based on positive clinical results, more active individuals with a desire to go beyond the limitations of the current implant system would be prospective candidates for the treatment. Recent developments of more advanced prosthetic legs, some of which have the capability to provide additional joint torques during loadbearing to compensate for lost musculature, will increase the demands on the strength of the implant system. It is believed that these types of prosthetic legs may function particularly well in combination with the e-OPRA Implant System.

2. Scope of thesis

The aim of this thesis was to introduce the neuromuscular interface of the e-OPRA Implant System to users with lower limb amputation and to simultaneously reduce the limitations on high impact loading that are currently placed on implant systems for bone-anchored attachment of prosthetic limbs. To achieve these objectives, this thesis project sought to:

- Increase the structural capacity the OPRA Implant System so that it can tolerate lower limb prosthetic usage at load levels beyond those associated with activities of daily living.

- Translate the neuromuscular interface of the e-OPRA Implant System for upper limb to the implant system for the lower limb.

- Prepare for clinical implantation of the developed system within a clinical investigation.

Within the scope of these objectives the following research questions have been addressed.

- What are the mechanical and biomechanical characteristics of implant systems that have showed successful results for bone-anchored attachment of limb prostheses?

- What is the load exposure of bone-anchored implants for amputation prostheses and surrounding bone during use?

- What would the load exposure of the bone-anchored implant and surrounding bone be if subjected to high loading activities which are beyond the recommendations of current implant systems?

- How is the loadbearing capacity of the bone-anchored implant affected by the surrounding bone tissue?

- How do geometrical design features affect the structural capacity of the bone-anchored implant system?

- To what extent can surface enhancement methods influence the structural endurance of the bone-anchored implant system?

Figure 1 illustrates the thesis project phases and the research output generated by the thesis.

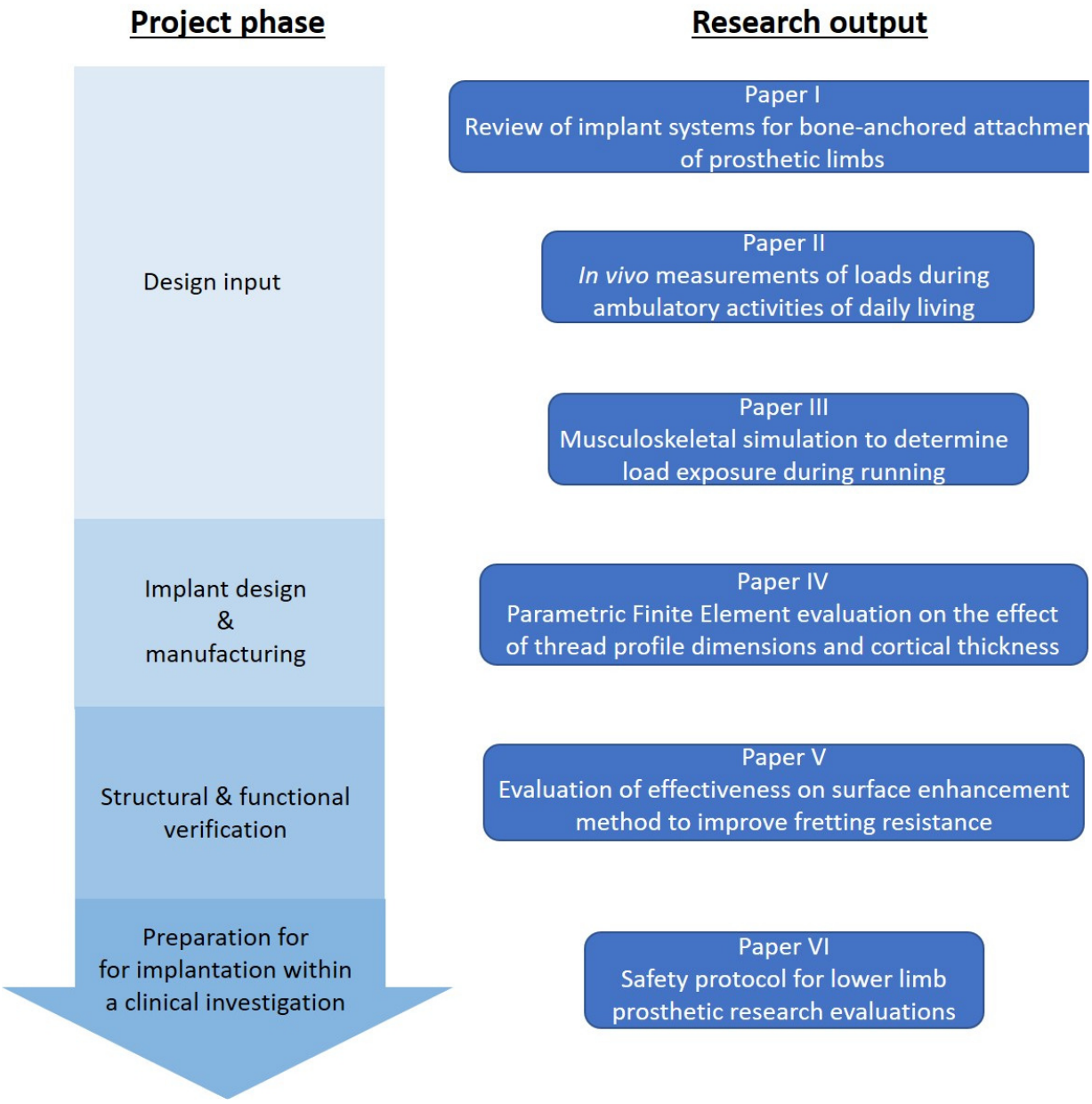

Figure 1. Thesis project phases and research output.

3. Background

3.1. Socket attachment of prosthetic limbs

The aim of a lower limb prosthesis is to restore the functions of the missing foot and leg of which the most important are bodily support, balance, and means of ambulation. The prosthesis is most commonly attached to the body via a socket which compresses the soft tissues of the residual limb. The prosthesis is kept in place via frictional forces between the socket and the residual limb. In the case of lower limb amputation, the prosthetic retention must withstand considerable forces and moments since the prosthetic leg is loaded with the full body weight of the user during ambulation [20]–[22]. This demands that the prosthetic socket has a good fit to the residual limb, high friction coefficients and substantial normal forces between the socket and the skin to prevent relative sliding at the interface. The socket fit may be negatively affected by residual limb volume changes due to edema, atrophy or changes in body composition, [23]. Volume changes may also occur temporarily due to changes in environmental conditions such as temperature and humidity, or as a consequence of muscle contractions within the residual limb during ambulation. Environmental factors and the activity level may affect the friction coefficients due to perspiration and the dryness of the skin. These factors can make it difficult to obtain a consistently good fit between the socket and the residual limb. For individuals with a short residual limb, skin disorders, heterotopic ossification, or other conditions which affects the residual limb, it may be very difficult to achieve a functional prosthetic attachment using a socket. Even in the absence of these conditions, pressure sores from excessive and prolonged pressure on certain parts of the soft tissue, blisters originating from the residual limb pistoning within the socket, or rashes from a humid contained environment can all result from sub-optimal socket attachment of the leg prosthesis and may lead to pain and reduced prosthesis usage [1]–[6].

3.2. Lower limb prostheses

A transfemoral prosthesis consists of separate knee and foot prostheses and a prosthetic pylon to connect the two to form a prosthetic leg. Knee prostheses can be divided into mechanical knees or microprocessor-controlled knees (MPK). Mechanical knees (sometimes also referred to as non-microprocessor knees) are entirely passive and the impedance of the knee joint is controlled by friction, hydraulics or a mechanical locking mechanism. In MPKs on the other hand, the joint impedance is dynamically adjusted by a microprocessor, based on kinematic and force/torque data received from sensors on the prosthesis. MPKs may be further divided into energetically passive MPKs or active MPKs, where only the latter provides net positive power to the user. Such energy output from the knee joint is required to be able to naturally perform activities such as stair and slope ascension or raising from a seated position. At the writing of this thesis, the only commercially available active MPK is the PowerKnee from Össur, Iceland. However, extensive research is being conducted on several other active prosthetic legs by numerous research groups, examples are the Open Source Leg developed at the University of Michigan, MI, USA [24], the Cyberlegs developed at Vrije University in Brussels, Belgium [25], [26], the Vanderbilt knee and ankle prostheses [27], [28] developed at Vanderbilt University in Nashville, TN, USA, the Hybrid knee developed at Research Institute of Chicago (now known as Shirley Ryan Ability Lab), and the active knee and ankle prostheses

developed at Massachusetts Institute of Technology, MA, USA [29]–[32]. Prosthetic feet may be categorized as non-articulated feet or articulated feet, where non-articulated feet may be further subdivided into solid ankle cushion heel (SACH) feet or energy storage and return (ESAR) feet. The SACH foot has a solid keel which does not provide any aid during the push-off phase of the gait cycle. ESAR feet have a leaf spring function achieved by molded carbon fiber plates which are compressed by the body weight of the user during the stance phase and then spring back to return energy to the user for propulsion. Articulated feet may be either single axis or multi-axis, to enable plantar-dorsiflexion only or a combination of plantar-dorsiflexion and inversion-eversion. Analogous to prosthetic knees, a subset of the articulated feet is microprocessor controlled prosthetic feet (MPF). As with the knee prostheses, the MPFs may be either passive or active. There is currently only one active MPF commercially available, Empower (formerly known as BioM) by Ottobock, Germany.

3.3. Lower limb prosthetic control

The lower limb movements during ambulation are cyclic in nature but vary between ambulation modes (e.g., level ground walking, stairs, ramp etc.). An ambulation mode may be divided into phases for example as indicated in Figure 2.

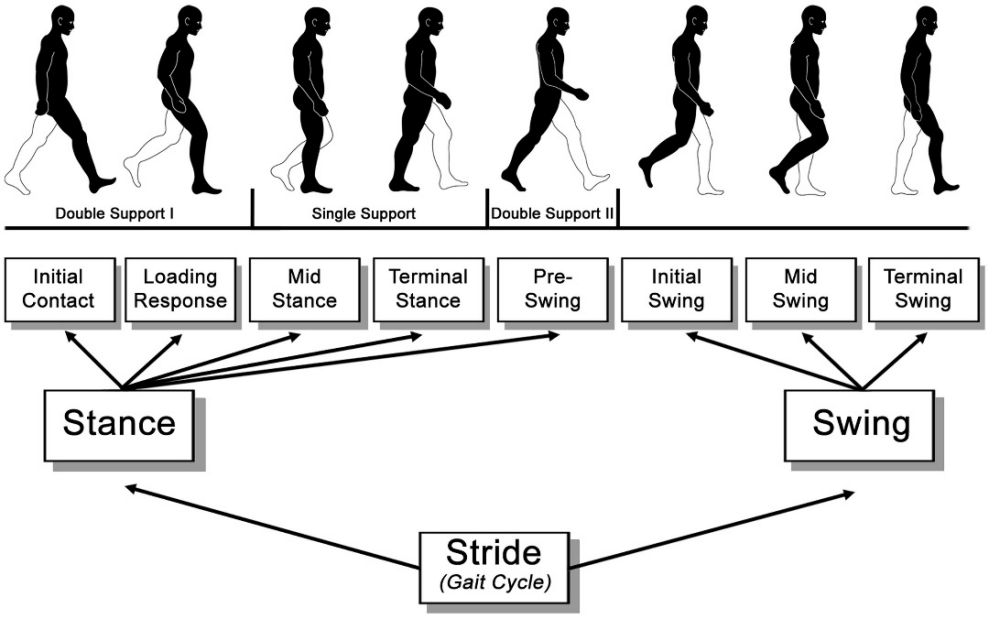

Figure 2. The figure (reproduced with permission from Stöckel et al. 2015 [33]*) shows the functional gait phases as defined by Perry and Burnfield 2010* [34].

In MPKs, the microprocessor uses sensor data to determine current gait phase and adjusts the impedance in real time according to predefined desired values for that gait phase. How the predefined desired values of the impedance vary with the gait phase is dependent on the ambulation mode. In order to determine the ambulation mode or detect transitions between ambulation modes, a high-level control scheme is used. This high-level control scheme may use additional data from sensors on the prosthesis, sensors placed on the sound limb, or biological signals such as EMG from the residual limb of the user to determine the ambulation

mode or transitions between different modes. If these detections can be consistently correctly performed, then the prosthesis user may ambulate with seamless transitions between different ambulation modes. For active MPKs the same control strategy may employed but with the knee torque as an additional variable. Active prosthetic components increase the number of possible ambulation modes and thus increases the complexity of the control scheme.

For non-cyclic movements, other control schemes based on direct control or pattern recognition may be used. The use of EMG data from the residual limb to control the prosthesis is a standard practice in upper limb prostheses but it is not yet commercially available for the control of lower limb prostheses despite research efforts with promising results [35]–[39]. One reason for this may be increased difficulties to achieve robust EMG signals due to instabilities in the skin-to electrode interface for example as a consequence of socket pistoning (i.e., the displacement of the residual limb relative to the socket in the distal-proximal direction). Another reason may be that many activities of daily living (e.g., ambulation) follow well-defined cyclic patterns which to a certain extent makes them possible to predict even in the absence of input from biological sensors.

3.4. Bone-anchored attachment of prosthetic limbs

It was to address the inherent problems associated with the socket attachment, that the method of bone-anchored attachment of prosthetic limbs was developed. With this concept, a percutaneous skeletal extension is created in a surgical procedure where an implant is placed with its proximal end inserted into the remainder of the residual bone and its distal end protruding through the skin. The prosthesis can then be attached directly to the external portion of the implant, thus eliminating the need for a socket. The first fully successful clinical attempt of this method dates back to 1990 when an individual with bilateral transfemoral amputation was treated with this method in Gothenburg, Sweden [40]. The positive result owes a large part of its success to osseointegration. The phenomenon, first coined by Brånemark *et al.* in 1977 [41] had been discovered already in the early 1960s by observing that bone tissue could form an exceptionally intimate and mechanically stable connection with titanium [8]. The first application of osseointegration was in the dental field, but it has since then spread to other applications such as hearing aids, facial reconstructions and orthopedic applications [10].

Accumulated knowledge from osseointegration in the dental field, meticulous research on the biomechanical characteristics of osseointegration [42]–[46] and the initial experiences of bone-anchored attachment of limb prostheses led to refinement of the implanted components and a standardized treatment protocol. The implant system received a CE-mark under the product name OPRA Implant System, manufactured by Integrum AB, Mölndal, Sweden. The system is CE-marked for transfemoral, transhumeral and thumb/finger amputations but custom-made implants are available for the aforementioned levels, as well as for transtibial and transradial amputations. The treatment has gained increasing clinical acceptance and is currently available in 12 countries. The OPRA Implant System was recently granted a premarket approval (PMA) by the Food and Drug Administration (FDA) in the USA for treatment at the transfemoral level.

Following the successful results in Sweden, another implant system was independently developed in Germany under the name of ILP (Integral Leg Prosthesis, ESKA Orthopaedic Handels GmbH, Lübeck, Germany) (also known as EEP (Endo-Exo Prosthesis). In 1999, the

first patient was treated with the ILP implant system, which is now in clinical use in Germany, the Netherlands, and Australia. Another system, based on the ILP design, was developed in Australia under the name of OPL (Osseointegrated Prosthetic Limb, Permedica s.p.a., Milan, Italy). This system is also clinically available in the Netherlands where it is called OFP (Osseointegrated Femur Prosthesis) or OTP (Osseointegrated Tibia Prosthesis) (manufactured by OTN Implants BV, The Netherlands). To date OPRA, ILP, and OPL are the only commercially available systems for direct skeletal attachment of external limb prostheses (Figure 3).

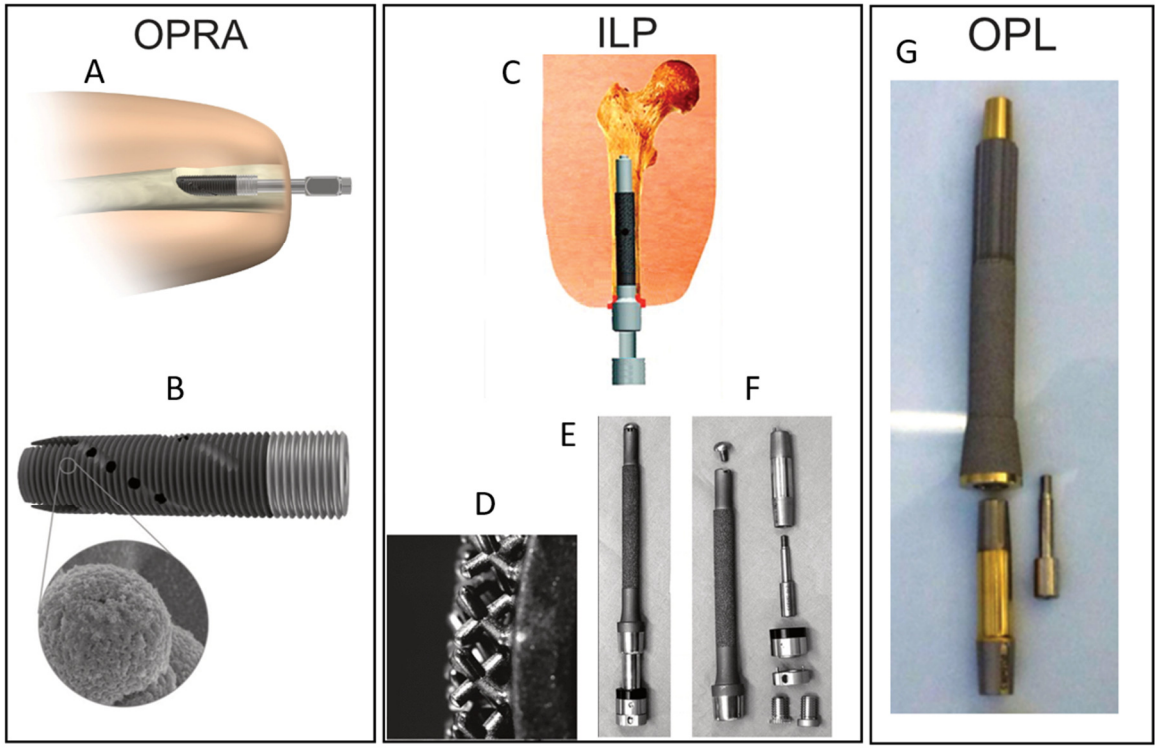

Figure 3. The figure (adapted with permission from Thesleff et al. 2018 [47] *(Paper I)) shows commercially available implant systems for bone-anchored attachment of prosthetic limbs. (A) Schematic image of OPRA Implant System in an amputated limb. (B) OPRA Fixture; the exterior surface in the dark grey region is treated to enhance osseointegration. The lower image shows a close-up of the laser-induced micro structure from the surface treatment. (C) Schematic image of the ILP implant system. (D) Close-up of the spongiosa metal surface to enhance osseointegration and ingrowth. (E) ILP implant system assembled. (F) Exploded view of ILP implant system assembly. (G) OPL type-B implant system.*

A number of other systems have reached the stage of clinical experiments in humans. These are the ITAP (Intraosseous Transcutaneous Amputation Prosthesis, Stanmore Implants Worldwide, Watford, United Kingdom) developed in the United Kingdom, the KWA (Keep Walking Advanced, Tequir S.L., Valencia, Spain) developed in Spain, and two systems developed in the United States: POP (Percutaneous Osseointegrated Prosthesis, DJO Global, Austin, USA) and COMPRESS (Zimmer Biomet, Warsaw, USA) (Figure 4).

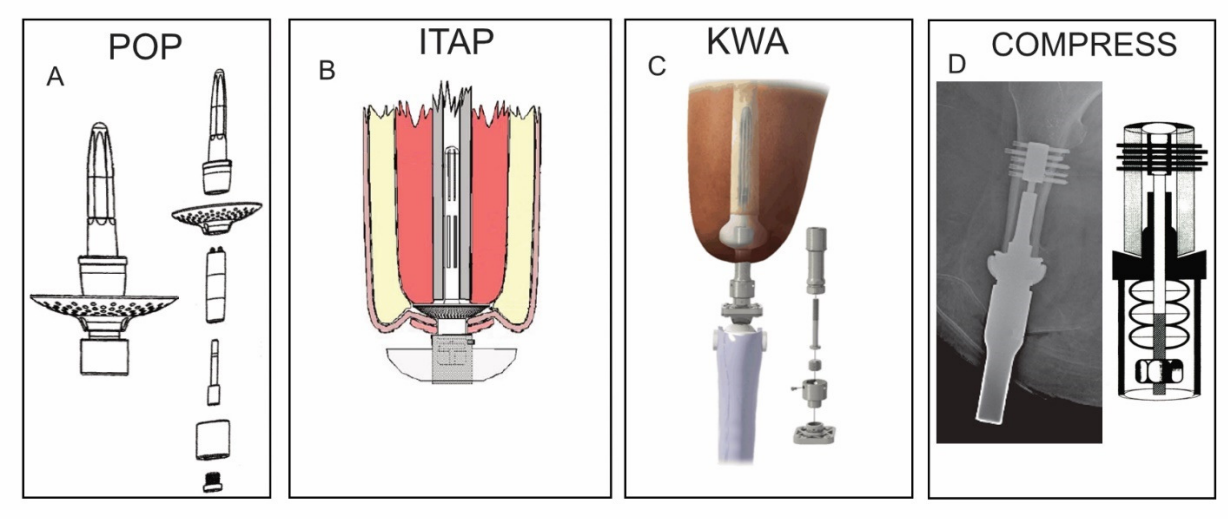

Figure 4. The figure has been adapted with permission from Thesleff et al. 2018 [47] *(Paper I). The figure shows implant systems for bone-anchored attachment of prosthetic limbs which have been successfully used in human subjects but are not commercially available. (A) Schematic illustration and exploded view of the POP system. (B) Schematic illustration of the ITAP system. (C) Schematic illustration of the KWA system. (D) Radiograph and schematic illustration showing the function of the COMPRESS system.*

None of the aforementioned systems have reached the clinical and regulatory maturity of the OPRA Implant System, which at the time of writing this thesis is the only system that has been granted a premarket approval in the USA.

3.5. Benefits of bone-anchored attachment of prosthetic limbs

With bone-anchored attachment of the prosthetic limb, the soft tissues in the residual limb are bypassed due to the elimination of the socket, and forces applied to the prosthesis are transferred directly to the skeleton. This leads to reduced energy dissipation and in individuals with transfemoral amputation it has been shown that bone-anchored attachment leads to a more efficient gait and reduced energy expenditure compared with socket attachment [48], [49]. For this patient group it has also been shown that bone-anchored attachment leads to improvement in quality of life, mobility, prosthesis usage, range of motion, sitting comfort, and reduced amputation- and prosthesis-related problems [48]–[55]. The rigid connection to the skeleton also provides mechanical stimuli to the bone which is needed to preserve the bone stock. Another positive consequence is osseoperception, which is the sensation arising from mechanical stimulation of a bone-anchored prosthesis [56]. Osseoperception is a multisensory perception involving tactile as well as auditory sensation. It has been shown that users with bone-anchored attachment of the prosthesis have improved ability to recognize vibrotactile information from the prosthesis compared with socket users [57], [58]. This may be particularly important for individuals with lower limb amputation since it increases the awareness of the surface structure of the ground and may potentially reduce the risk of falling. Bone-anchored attachment also leads to a faster and simpler donning and doffing procedure of the prosthesis compared with socket prostheses.

3.6. Current OPRA Implant System

The current version of OPRA Implant System, (Figure 5), consists of three components: (1) an externally threaded, cylinder-like, fully implanted “fixture”; (2) a percutaneous skeletal extension called “abutment”; and (3) an “abutment screw”. The proximal end of the abutment is press-fit into the distal end of the fixture and the distal end protrudes through the skin and allows for connection of the prosthesis. The abutment screw extends through the hollow center of the abutment to clamp the abutment and the fixture together by a preload via the proximal thread engagement to the fixture and the abutment screw head on the distal end of the abutment. For lower limb amputations, the fixture is implanted 20 mm countersunk into the bone as indicated in Figure 5. This is done to address the problem of distal bone resorption, which was sometimes observed when the fixture was placed flush with the distal bone end, and to reduce the risk of infection in the bone-fixture interface [59]–[61]. The system is designed to ensure that the abutment and abutment screw fracture before the fixture, or the bone, if exposed to excessive loads, since these components are more easily replaced than the osseointegrated fixture.

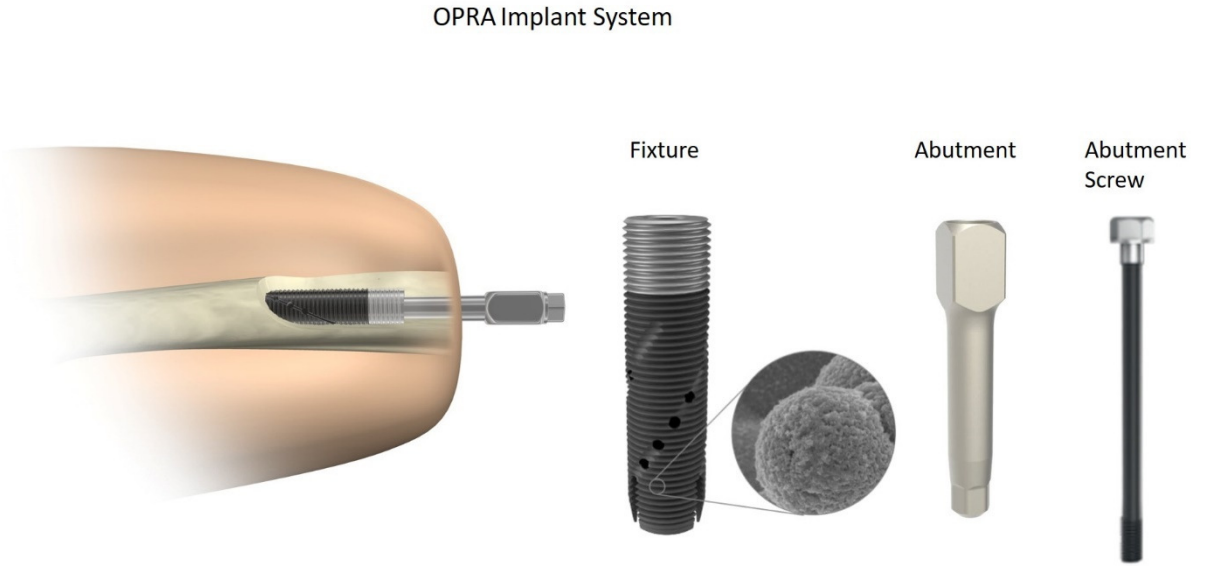

Figure 5. OPRA Implant System and its individual components.

3.7. Safety release Axor II

The direct connection between the skeleton and the prostheses makes excessive loads hazardous with the risk of implant or bone fracture in case of a fall. To prevent such failures, the OPRA Implant System at the lower limb level is equipped with an external safety system. It is an intermediate connector between the percutaneous skeletal extension and the external prosthesis, and it automatically releases the connection in response to overloading. For transfemoral amputations, this system, known as the Axor II (Figure 6), has active release functions responding to overloads both in bending and in torsion. The release thresholds are set to ensure that no potentially harmful moments are transferred to the implant and the bone while at the same time being sufficiently high to prevent inadvertent release during activities of daily living.

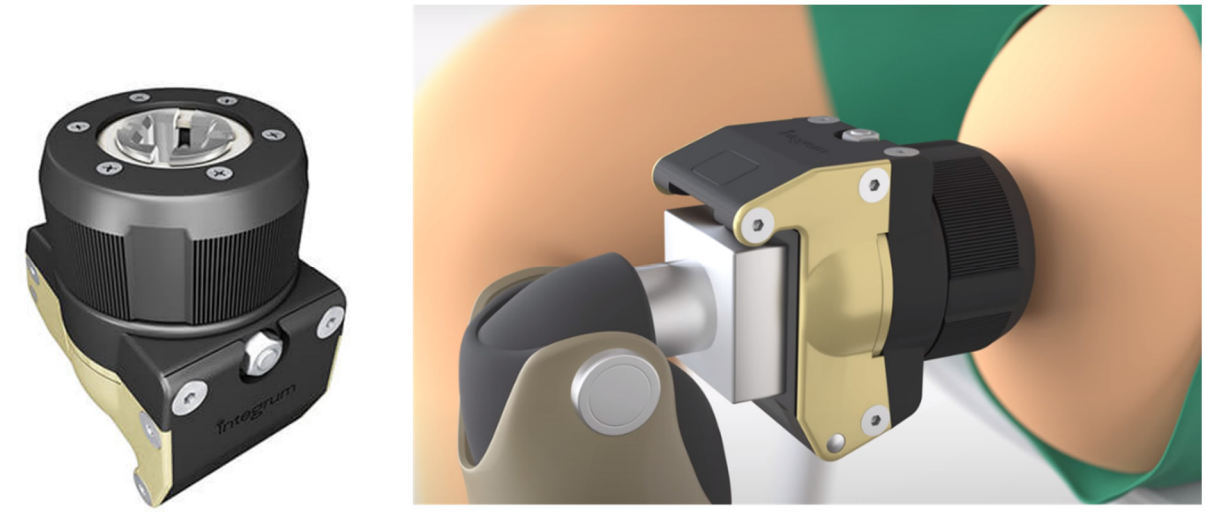

Figure 6. Axor II, the safety release system to be used in combination with the OPRA Implant System at the transfemoral level.

3.8. Current e-OPRA Implant System

The e-OPRA Implant System (Figure 7) is an enhanced version of the OPRA Implant System, where the enhancement consists of a neuromuscular interface realized by implanted electrodes placed into/onto muscle tissue and around nerves in the residual limb [11], [12]. The e-OPRA Implant System is connected to the skeleton, muscles, and nerves within the residual limb and forms a neuromusculoskeletal interface. The percutaneous titanium implant is used as a permanent stable human-machine gateway for wired communication between muscles and nerves inside the body and the prosthesis external to the body. The implanted electrodes record myoelectric activity and this information is used to provide voluntary control of the prosthetic limb [11]–[15]. The system also supports communication in the opposite direction, where signals from pressure sensors on the external prosthesis may record contact of an object, and the system responds by providing electrical stimulation via the neural interface, eliciting a physical sensation as originating in the missing limb [11], [12], [16].

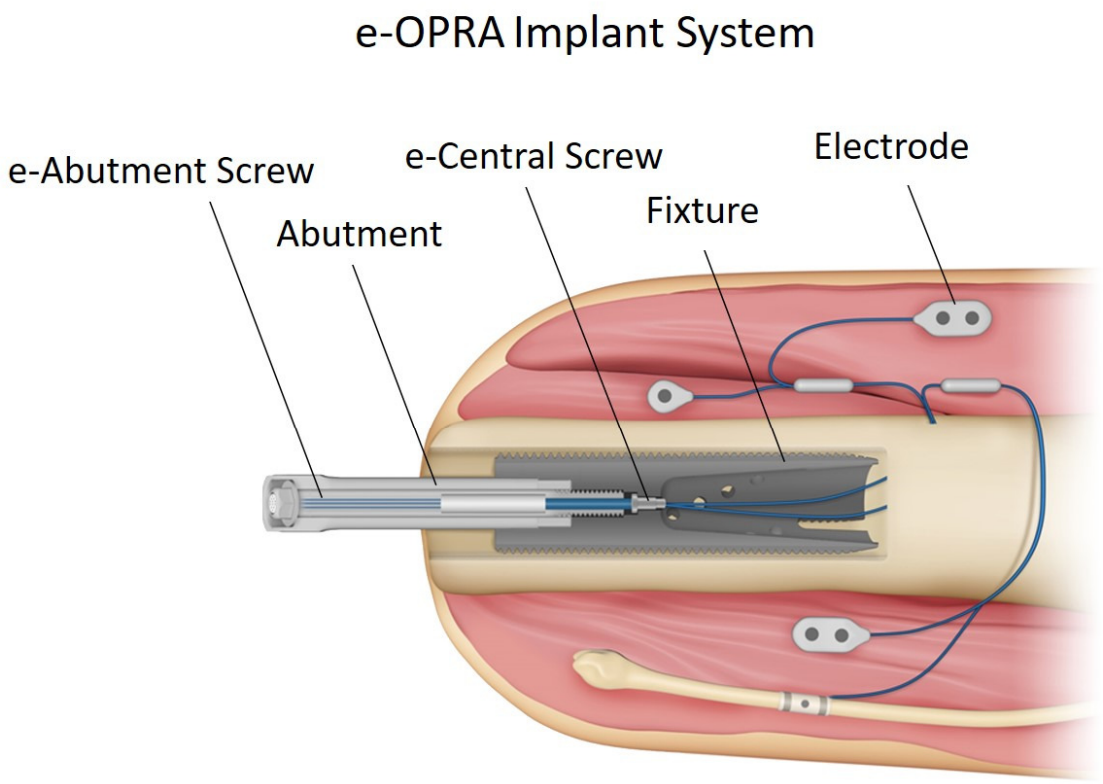

Figure 7. Schematic cross-sectional view of the e-OPRA Implant System.

The structural components of the system, namely the fixture and the abutment, are unchanged from the OPRA Implant System whereas the e-abutment screw and the e-central screw have been modified with respect to their OPRA counterparts. Specifically, they have been equipped with in-line connectors which ensures a wired electrical connection from the implanted electrodes to the distal end of the abutment screw. The e-OPRA Implant System has preserved the modularity from the OPRA Implant System, which allows for replacement of individual components if needed. The e-OPRA Implant System was implanted for the first time in 2013 in a 40-year-old man with transhumeral amputation [11]. He has since then been using the system continuously in his daily life. The system has also been implanted in five more individuals with upper limb amputation (four at the transhumeral level and one at the transradial level) as part of an ongoing clinical trial, and it has been shown that a prosthesis connected to the skeleton, nerves, and muscles, improves function and quality of life of people with upper limb amputations [12], [14], [16], [62]. The e-OPRA Implant System has no precedents in the field and is one of the most integrated bionic systems in the word. The collective experience leads to the expectation that this neuromusculoskeletal interface in combination with advanced leg prostheses, could provide significant improvements in prosthesis control and function also for individuals with lower limb amputation.

3.9. Recent advancements in surgical techniques for improved prosthesis control

A number of promising surgical techniques have been developed in recent years by which the amputated limb is surgically modified to increase the capacity for extraction of control information. One such example is targeted muscle reinnervation (TMR). As a result of an amputation, a nerve may be severed and deprived its muscular target. After being severed, the nerve may still carry motor control information but the small amplitude of the signals makes it difficult to use them for prosthesis control [63]. However, by redirecting the severed nerve to a new target muscle, the nerve will innervate the muscle which will in turn serve as a biological amplifier of the motor control information that is sent via the nerve. The EMG signals can be recorded by electrodes and may thus be used for prosthesis control. For successful results, the new target muscle should be denervated from other motor nerves which may otherwise generate unwanted EMG signals which can confound prosthesis control [63]. TMR was first clinically implemented by Kuiken *et al.* in 2003 on an individual with bilateral shoulder disarticulation [64]. The method has also been used for prosthesis control in individuals with lower limb amputation [35]. TMR is also investigated for treatment of painful neuromas which may arise as a result of an amputation [63].

A related surgical technique is the regenerative peripheral nerve interface (RPNI) [65]. With this method, a transected peripheral nerve or peripheral nerve fascicle is implanted into a free muscle graft [66]. After undergoing reinnervation by the nerve and revascularization, the muscle graft functions as a bio amplifier to produce myoelectric activity which can be recorded with implanted electrodes and used for prosthesis control. Since free muscle grafts are used, and due to the fact that the nerve may be split into several fascicles, each implanted into a separate muscle graft, RPNIs may provide a larger number of EMG signal sources for prosthetic control compared with TMR.

A third recently developed surgical technique is known as agonist-antagonist myoneural interface (AMI). With this technique agonist-antagonist muscle pairs are created within the residual limb. The muscle pairs are created so that a contraction of the agonistic muscle induces tension of the antagonistic muscle and vice versa. The muscle stretch generates proprioceptive information which in addition to EMG signals used for prosthetic control can provide proprioceptive feedback which may enhance the ability to control the prosthesis [67]–[71].

4. Design input

4.1. Systematic literature review – Paper I

As part of the design input phase of this thesis project, the design features and biomechanical characteristics of known implant systems for bone-anchored attachment of limb prostheses were studied in detail in a systematic literature review [47] (Paper I). All the studied systems had shown some level of clinical success, defined as successful loadbearing function for at least one year after implantation. A common feature for the implant systems is that they all use intramedullary implants. However, large differences were found in how primary and secondary stability was achieved. For the primary stability, defined as the immediate stability before healing and osseointegration, one of three strategies were used: a threaded connection (OPRA), axial compression (COMPRESS), or a press-fit connection (the rest of the systems). For the secondary stability, all implant system used variations of porous surfaces for bone ingrowth. Regarding the implant material, all studied systems used the titanium alloy Ti6Al4V as the bulk material, except for the ILP which uses a cobalt chromium molybdenum alloy. A comparison of material and interface characteristics between the systems is presented in Table 1.

Table 1. The table (adapted with permission from Thesleff et al. [47] *(Paper I)) shows a comparison of material and interface characteristics of bone-anchored implant systems for direct skeletal attachment of external limb prostheses.*

		Interfaces		
System	**Material**	**Bone – Implant**	**Implant – Percutaneous part**	**Percutaneous part – Soft tissue**
OPRA	Ti6Al4V	Thread	Press-fit and locking screw	Polished
ILP	CoCrMo	Press-fit	Press-fit and locking screw	Polished
OPL	Ti6Al4V	Press-fit	Press-fit and locking screw	Polished
ITAP	Ti6Al4V	Press-fit	-	Perforated flange / Polished
POP	Ti6Al4V	Press-fit	Press-fit and locking screw	Ceramic coating
COMPRESS	Ti6Al4V	Transverse pins / Axial compression	Taper connection	Porous titanium / Polished
KWA	Ti6Al4V	Press-fit	Press-fit and locking screw	Polished

4.2. Materials

This section provides a brief introduction to bone tissue and the femur with regards to its mechanical properties and structural capacity. This is followed by a short description of potential implant materials and their characteristics in terms of mechanical properties, biocompatibility, and durability.

4.2.1. Bone tissue

Bone tissue is the hard organic compound from which our skeletons are made and its basic function is to provide structural support for our bodies. At a macroscopic level, the material bone is divided into two categories: trabecular bone, also commonly referred to as cancellous or "spongy" bone, and cortical bone, also known as compact bone. These two types of bone have the same material building blocks, a mineral phase which mainly consists of hydroxyapatite, an organic phase with collagen type-I as the major constituent and water. What distinguishes cortical bone from trabecular bone is the structure and the porosity of the material. Trabecular bone has a high porosity, typically 75-95% [72] and the structure can be described as a porous bone matrix of interconnected plates and struts. Cortical bone instead is a compact material and has a much lower porosity, normally about 5-10% but increases with age and osteoporotic diseases [72]. As a result of their different structure and porosity, the two bone types exhibit large differences in their macroscopic mechanical behavior. Because of its compact structure, cortical bone is much stiffer and stronger than trabecular bone, whereas trabecular bone may deform more before fracturing.

4.2.2. Bone remodeling

Bone is not a static tissue but is continuously undergoing changes as the result of the interplay between bone resorption, where bone tissue is removed, and new bone formation. The result from these competing processes is called bone remodeling. The remodeling process is dependent on mechanical loading, where new bone formation and bone resorption is regulated in response to the loads that the bone has to withstand. It can be viewed as an optimization process, where the objective is to minimize the weight, while being sufficiently strong to safely withstand repeated external loads. If the mechanical stimuli are low, resorptive activity will dominate to reduce the bone mass, leading to net bone loss. If on the other hand, the bone receives high repeated mechanical stimuli, new bone formation will dominate and increase the bone mass until a bone homeostasis is reached.

4.2.3. Mechanical properties of bone

On a macroscopic level, trabecular bone has isotropic material properties whereas cortical bone can be adequately modelled with orthotropic or transversely isotropic material properties. Bone is a viscoelastic material and thus has rate dependent material properties. At high strain rates bone is stiffer and stronger than at low strain rates. Wolfram and Schwiedrzik in 2016 published a review of prior reseaerch studies, reporting experimentally measured yield and ultimate strength and strain of human cortical bone [73]. From these studies ultimate strengths of 54–166 MPa and 106–204 MPa have been reported for uniaxial tension and compression

respectively. Reported values for the ultimate shear strength in the longitudinal direction have been 29–68 MPa according to the same literature review [73]. The ranges come from 23 different studies with variations in experimental conditions and test specimens. In Table 2, the experimentally determined mechanical properties of human cadaver femora from two of the included studies are presented.

Table 2. Experimentally measured properties for human femur cortical bone. E denotes the elastic modulus. G denotes shear modulus. ν denotes Poisson's ratio. σ denotes ultimate normal stress. τ denotes ultimate shear stress. Subscripts L, and T, denotes the longitudinal direction and the transverse plane respectively.

Author & Year	Test specimens & Test method	Material properties	Ultimate strength
Reilly 1975 [74]	Human femur Uniaxial testing at 2-5%/s Torsional testing (rate not stated)	E_L = 17 GPa E_T = 11.5 GPa G_{LT} = 3.28 GPa ν_{TT} = 0.58 ν_{LT} = 0.46	$\sigma_{L\ Tension}$ = 133 GPa $\sigma_{L\ Compression}$ = 193 GPa $\sigma_{T\ Tension}$ = 51 GPa $\sigma_{T\ Compression}$ = 133 GPa τ_{LT} = 68 GPa
Dong 2004 [75]	Human femur Uniaxial testing at 0.1%/s Torsional testing at 1°/s	E_L = 16.61 GPa E_T = 9.55 GPa G_{LT} = 4.74 GPa ν_{TT} = 0.46 ν_{LT} = 0.37	

The strength and the Young's modulus (elastic modulus in tension) for trabecular bone is highly dependent on the porosity and apparent density, therefore it is difficult to set a well-defined value for the strength, and the Young's modulus, but mid-range values as design goals for replacement materials of trabecular bone are 5-10 MPa strength and 50-100 MPa Young's modulus according to Yaszemski *et al.* 1996 [76].

4.2.4. Bending and torsional strength of the femur

The bending strength of femur has been determined in a number of studies on human cadaver bones using 3-pt bending and 4-pt bending tests in quasistatic or dynamic conditions. The reported failure moments at the diaphysis range from 125–202 Nm and 185–310 Nm in quasistatic conditions for females and males respectively. For dynamic conditions, the reported failure ranges are 298–435 Nm and 355–605 Nm for females and males, respectively [77], [78]. Fewer studies have been performed to determine the torsional strength of the femur, however Robertson *et al*. 2007 [79] reported a torsional strength of 132 ± 33 Nm for intact femurs in an experimental study on 12 femurs (5 female, 7 male, age 59 ±16 years).

4.2.5. Orthopedic implant materials

Materials for orthopedic implants must be biocompatible due to their permanent implantation in the body. The human body is a corrosive environment and thus a high corrosion resistance is imperative. For loadbearing implants, a high strength and fatigue resistance is also important to prevent implant failure. Most loadbearing implants have a much higher Young's modulus than the surrounding bone tissue. This can lead to a phenomenon known as stress-shielding

where the implant shields the bone tissue from experiencing the stresses associated with typical loading with a potential consequence of bone resorption and reduced bone density. To prevent this from happening, a low Young's modulus is desired. For modular implants, the wear resistance is also important since wear debris from contact surfaces may cause adverse local tissue reactions, resorption and aseptic loosening of the implant [80]–[82]. A good resistance to wear and a related phenomenon known as fretting is also necessary to preserve the stability in static connections between the implanted components. Fretting is defined as small amplitude oscillatory movement between contacting surfaces that are nominally at rest [83]. The relative movement may lead to fretting corrosion by disruption of protective passive oxide films of the surfaces and thereby make them more susceptible for corrosion [80]. The damage from the fretting action accelerates nucleation and early growth of fatigue cracks, reducing the mechanical strength and durability under continued loading [83]. The aforementioned desired characteristics limits the number of materials that are suitable for loadbearing orthopedic implants. The most commonly used materials are, commercially pure titanium or titanium-based alloys, cobalt-chromium-based alloys or stainless steel 316L [84]. These materials are briefly discussed below.

4.2.5.1. Stainless steel

Steel has a density of approximately 8000 kg/m3 and a Young's modulus of 200 GPa. Only austenitic and precipitation hardened stainless steels are used in orthopedic applications [84]. Most widely used is AISI 316L which is an austenitic stainless steel where 'L' indicates low carbon content (< 0.03 %). Despite good biocompatibility, high strength and relatively low cost this type of steel is not as popular as titanium-based and cobalt-chromium-based alloys for permanent loadbearing implant applications [85].

4.2.5.2. Titanium and titanium-based alloys

Titanium is a very bioinert material due to a highly corrosion-resistant oxide layer which is rapidly formed on the titanium surface. Other desirable features of titanium are the relatively low values of Young's modulus (115 GPa) and density (4500 kg/m^3) compared with steel and cobalt-chromium alloys. Titanium is also known for its excellent capacity for osseointegration. Both commercially pure titanium and titanium alloys are used for orthopedic implants. For applications requiring a high strength, the alloy Ti6Al4V (Al and V stands for aluminum and vanadium respectively) is most popular, due to its high yield and tensile strengths (yield strength ≥ 795 MPa and tensile strength ≥ 860 MPa [86]).

4.2.5.3. Cobalt-chromium based alloys

Of the cobalt-chromium-based alloys, CoCrMo (Mo stands for molybdenum) is the one which is most commonly used for loadbearing orthopedic implants. The excellent corrosion resistance and high strength (yield strength minimum 827 MPa and tensile strength minimum 1192 MPa [87]) are the main reasons for its suitability for these applications.

4.3. Loading of the bone-anchored implant

High impact loads of magnitudes approaching the yield strength of the bone or the implant are prevented from reaching the implant by the external safety release system. However, it is crucial that the thresholds of the safety release mechanism are sufficiently high so that it does not release during intentional loading. Forces and moments under the thresholds, are transferred to the implant system and could potentially lead to fatigue of the implant or the bone if stress levels / load cycles exceed what the material can withstand. The loads may also influence remodeling of surrounding bone tissue which could affect implant and bone integrity over time.

4.3.1. Load measurements during everyday ambulatory activities – Paper II

To quantify the loading of the bone-anchored implant, a number of research studies have performed direct load measurements at the interface between the abutment and the prosthesis in individuals with the OPRA Implant System at the transfemoral level [88]–[92]. The most extensive dataset was collected within the scope of this thesis in Paper II [92] where load measurements were conducted on 20 individuals with the OPRA Implant System while performing everyday ambulatory activities. A summary of the obtained load data is presented in Table 3.

Table 3. Average (across research participants) peak (magnitude) force, and moment, during everyday ambulatory tasks from the study described in Paper II [92]. *F_A, F_{ML}, F_L denotes the peak forces along the anterior-posterior, medio-lateral and inferior superior directions respectively. M_A, M_{ML}, M_L denotes peak moments in the anterior-posterior, medio-lateral, inferior-superior directions respectively. M_B denotes the peak bending moment.*

	Walk	Slope Ascent	Slope Descent	Stairs Ascent	Stairs Descent
F_A [N]	101	106	93.6	77.2	102
F_{ML}[N]	75.2	69.7	66.8	67.1	54.9
F_L [N]	625	582	596	656	516
M_A [Nm]	30.7	27.4	27.4	24.3	19.7
M_{ML} [Nm]	18.7	18.8	20.4	20.9	20.1
M_L [Nm]	5.28	5.34	4.03	5.08	4.06
M_B [Nm]	36.7	34.5	35.4	33.0	32.2

4.3.1.1. Conclusions from Paper II

- Given the magnitudes of the measured forces and moments, the bending moment contributes the most to the overall stress state in the bone-anchored implant and surrounding bone.

- With reference to level ground walking, no activity generated statistically significantly higher bending moments on the bone-anchored implant and only stair ascent generated statistically significantly higher resultant force. For the majority of the research participants, the loads generated during level ground walking were of similar magnitude as the loads generated during other activities.

- There was a high variability in the measured loads between research participants.

- Using a crutch in the contralateral hand during level ground walking on average led to 10 % reduction in the maximum resultant force and 13 % reduction in the maximum bending moment across the research participants.

4.3.2. Loads during running – Paper III

With a stronger implant system, the limitations on what activities the user may perform could be reduced. One activity which is currently advised against is running. Running is a cyclic activity, causing repetitive loading on the implant and the bone. For long distance runners the number of load cycles may be large and could thus potentially lead to fatigue of the implant or the surrounding bone. The load exposure of the implant and the bone during running is not known. Load measurements from a similar scenario but with a distal femoral replacement rather than an implant for attaching a limb prosthesis was reported in a case study by Taylor and Walker in 2001 [93]. The distal femoral implant was instrumented to measure axial force, torque, and bending moments in the prosthesis shaft. The maximum reported load magnitudes for the study participant who weighed 70 kg, were 73 Nm and 51 Nm around the antero-posterior and medio-lateral axes, respectively, and 8.8 Nm torsional moment during jogging at 1.70 - 1.92 m/s. In another study by Taylor *et al.* in 2020 [94], an attempt was made to estimate the loads based on inverse dynamics from kinetic and kinematic data from able bodied participants running at self-selected speed. In that study, the average peak moments during running were approximately 140 Nm and 8 Nm in bending and torsion, respectively.

Due to the limited data and the fact that, for safety reasons, it is not possible to do direct measurements on the existing cohort of current users of OPRA Implant System during running, it was decided to conduct a simulation-based study to estimate the forces during running. A musculoskeletal simulation study was therefore performed using the publicly available software OpenSim [95]. Starting from a musculoskeletal model developed by Hamner *et al.* 2010 [96], an adapted model was created, where the lower limb segments and musculature were adapted to simulate an individual with a transfemoral amputation treated with a bone-anchored prosthesis. A non-articulated joint was created at the bone-implant interface to allow for force and moment data extraction. Following the OpenSim workflow (Figure 8), the adapted model was scaled and matched with a kinematic and ground reaction force dataset obtained from the study by Hamner *et al.* [96], where an able-bodied participant was running at 3.96 m/s on an instrumented treadmill. Using the OpenSim procedures of residual reduction algorithm, static optimization and joint reaction analysis, the loads at the simulated bone-anchored interface were extracted.

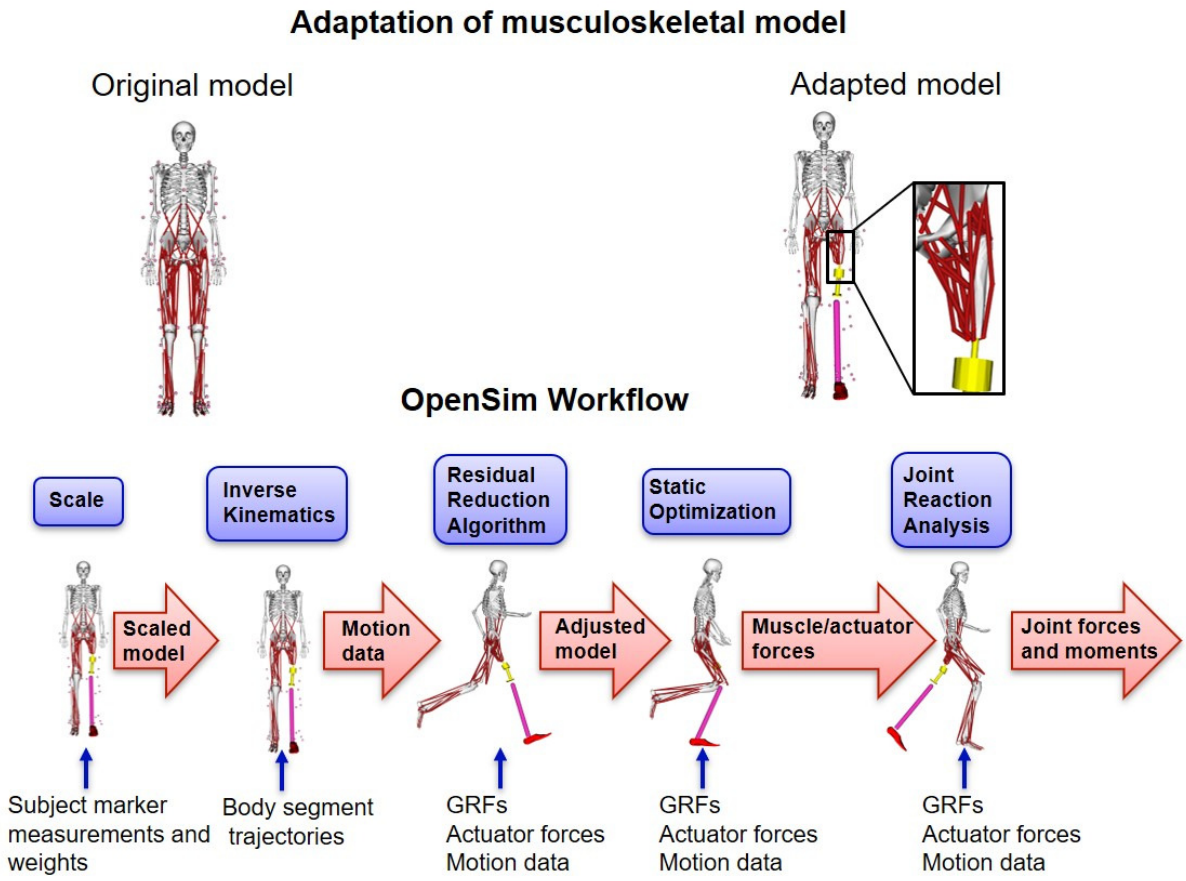

Figure 8. Procedures in the simulation-based investigation to determine the loads at bone-anchored implant during running [97] *(Paper III). The original musculoskeletal model and the dataset of an able-bodied individual performing a running trial on an instrumented treadmill were obtained from Hamner et al.* [96]*. By replacement and adjustment of lower limb segments and musculature of the amputated side, an adapted model simulating an individual with a transfemoral amputation treated with a bone-anchored prosthesis was created. A non-articulated joint was created at the bone-implant interface to allow for force and moment data extraction. The OpenSim workflow was performed in sequence as indicated. Details about each step of the procedure is available in Paper III* [97].

4.3.2.1. Results from Paper III

The results from the joint reaction analysis are presented in Figure 9 and in more detail in Paper III [97].

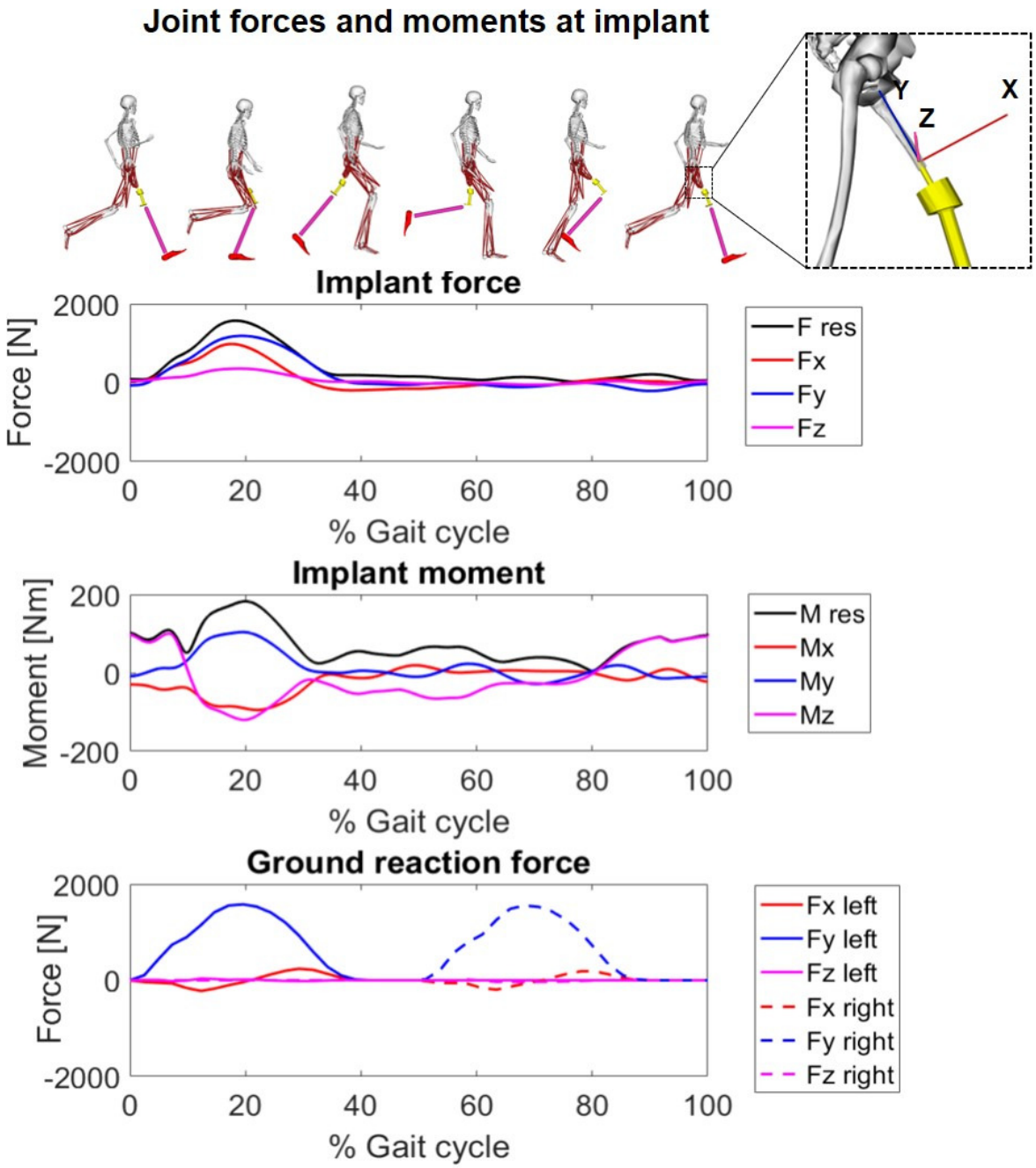

Figure 9. Force and moment data extracted at the bone-implant interface during a running gait cycle in Paper III [97]. *The forces and moments are presented in the local coordinate system of the bone-anchored implant in the left leg of the musculoskeletal model. The x-direction denotes the local anterior direction, the y-axis denotes the longitudinal direction of the bone-anchored implant (coincident with the longitudinal direction of the femur at the level of the amputation). The z-axis denotes the medial direction of the bone-anchored implant.*

4.3.2.2. Conclusions from Paper III

- The maximum bending moment at the bone-implant interface was 151 Nm.

- The model has several limitations which may affect the accuracy of the results. Examples of limitations are:
    - Uncertainties in the accuracy of the adapted model with respect to inertial properties of adapted leg segments, removal and adjustment of muscles trajectories and muscle properties).
    - Inherent uncertainty of using inverse dynamics for calculation of forces and moments at proximal joints.
    - Data set from able-bodied individual was used to calculate forces and moment in a model of a subject with transfemoral amputation.
    - Residual (nonphysical) forces and moments were required to fulfill Newton's second law of motion while keeping trajectory errors at minimum.

- The maximum torsional moment at the bone-anchored implant in the simulation was 100 Nm. This is an order of magnitude higher than the torsional moments reported during jogging and running in the studies by Taylor and Walker [93] and Taylor *et al.* [94], and during walking in Thesleff *et al.* [92], Lee *et al.* [88] and Frossard *et al.* [90]. Due to the uncertainty and potential sources of errors listed above, the results from this simulation study should be interpreted with caution.

5. Implant design

Safety was the highest priority in the implant design process. Therefore, efforts were made to preserve features from the OPRA Implant System that had proved to be well-functioning and had shown good results clinically. It was also decided to preserve the modularity of the system to ensure that a single failed component would not risk the entire system. Following concept generation and brainstorming sessions, potential implant system concepts were modelled in CAD for further evaluation. The concepts were subsequently evaluated in terms of mechanical strength using Finite Element Analysis (FEA). This was performed in an iterative process where the effect of specific design features was investigated to achieve an optimal implant system design. As part of this evaluation, a parametric study was performed to quantify the structural effects of dimensional changes of the thread profile and the cortical thickness of the surrounding bone [98] (Paper IV).

5.1. Parametric Finite Element Evaluation – Paper IV

The objective of the study was to perform a parametric evaluation on the effect of thread profile parameters and cortical thickness, on the peak stress and strains in a generic implant model subjected to external loads corresponding to average and high ambulatory loading. An additional aim was to quantify effects of changes in bone stiffness characteristics and distal bone resorption on the maximum stresses in the implant system. The generic model geometry and the investigated parameter space is presented in Figure 10.

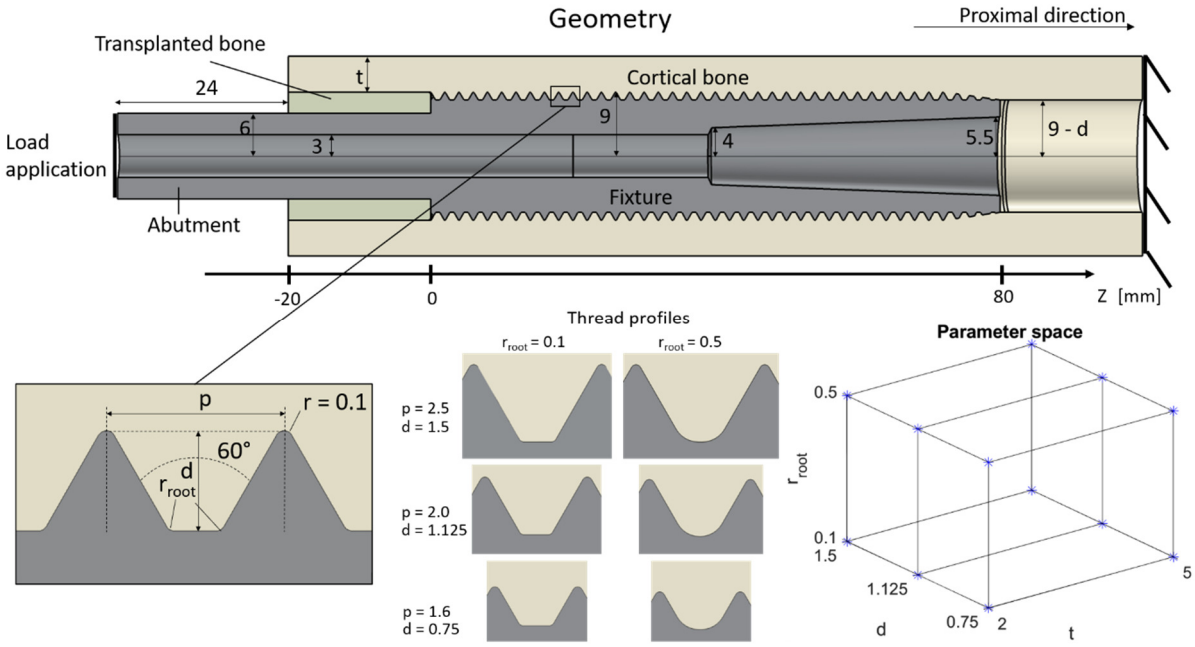

Figure 10. Generic geometry and the investigated parameter space in [98] *(Paper IV). The parameters evaluated within the investigation were the cortical thickness, t, the thread depth, d, and the fixture thread root radius, r_{root}.*

5.1.1. Conclusion from Paper IV

- Of the investigated parameters the cortical thickness had the largest effect on stress and strain in the cortical bone and the fixture. At loads corresponding to high loading ambulation, 5 mm of cortical bone thickness led to approximately 40 % lower maximum longitudinal stresses at the central half of the fixture compared with a cortical thickness of 2 mm.

- Changes in thread depth had larger effect on the maximum stresses in the fixture and the bone than changes in thread root radius within the evaluated parameter space.

- Stress reductions in the abutment were obtained by autologous transplantation of bone tissue distal to the fixture.

- A reduction in the longitudinal Young's modulus of the cortical bone had a larger relative effect on the maximum stress in the fixture at a large cortical thickness than at a small cortical thickness.

- Severe distal bone resorption, to an extent which leaves a portion of the distal fixture without support from cortical bone, may lead to more than 50 % increase in the maximum stress in the fixture as compared with a scenario with full support of cortical bone with 2 mm cortical thickness.

6. Structural and functional verification

Both static and dynamic testing of prototypes have been performed within this thesis project. The aims of this testing were both to determine the ultimate strength of the system and to determine the load limits during fatigue loading.

Unfortunately, no standard exists for testing of bone-anchored implants for attachment of limb prostheses. For the endurance tests, a modified version of a standard developed for endurance testing of the neck region of stemmed femoral components in hip implants has therefore been followed [99].

At the writing of this thesis, the full series of endurance tests has not been completed. However, preliminary results are encouraging and indicate substantial improvements in load capacity compared with current version of the OPRA Implant System.

6.1. Evaluation of surface enhancement method – Paper V

As part of the structural verification, a potential surface enhancement method for improved fretting resistance was experimentally evaluated [100] (Paper V). Fretting corrosion and fretting fatigue are known problems of modular orthopedic implants both due to negative tissue reactions from the wear debris and due to premature fractures of the implant itself as a result of the fretting degradation [80]–[82]. The investigated surface enhancement method, known as low plasticity burnishing (LPB), introduces compressive residual stresses in the treated region. These compressive stresses act against tensile loads and may thereby prevent or delay crack initiation from fretting or fatigue. The surface enhancement method was evaluated on a version of the first generation of the OPRA Implant System rather than on the new version of the implant system, since this method may be applicable also for this older version of the implant system in order to prolong fatigue life and improve fretting resistance.

The tested components, a schematic illustration of the surface enhancement process, and the test setup are presented in Figure 11.

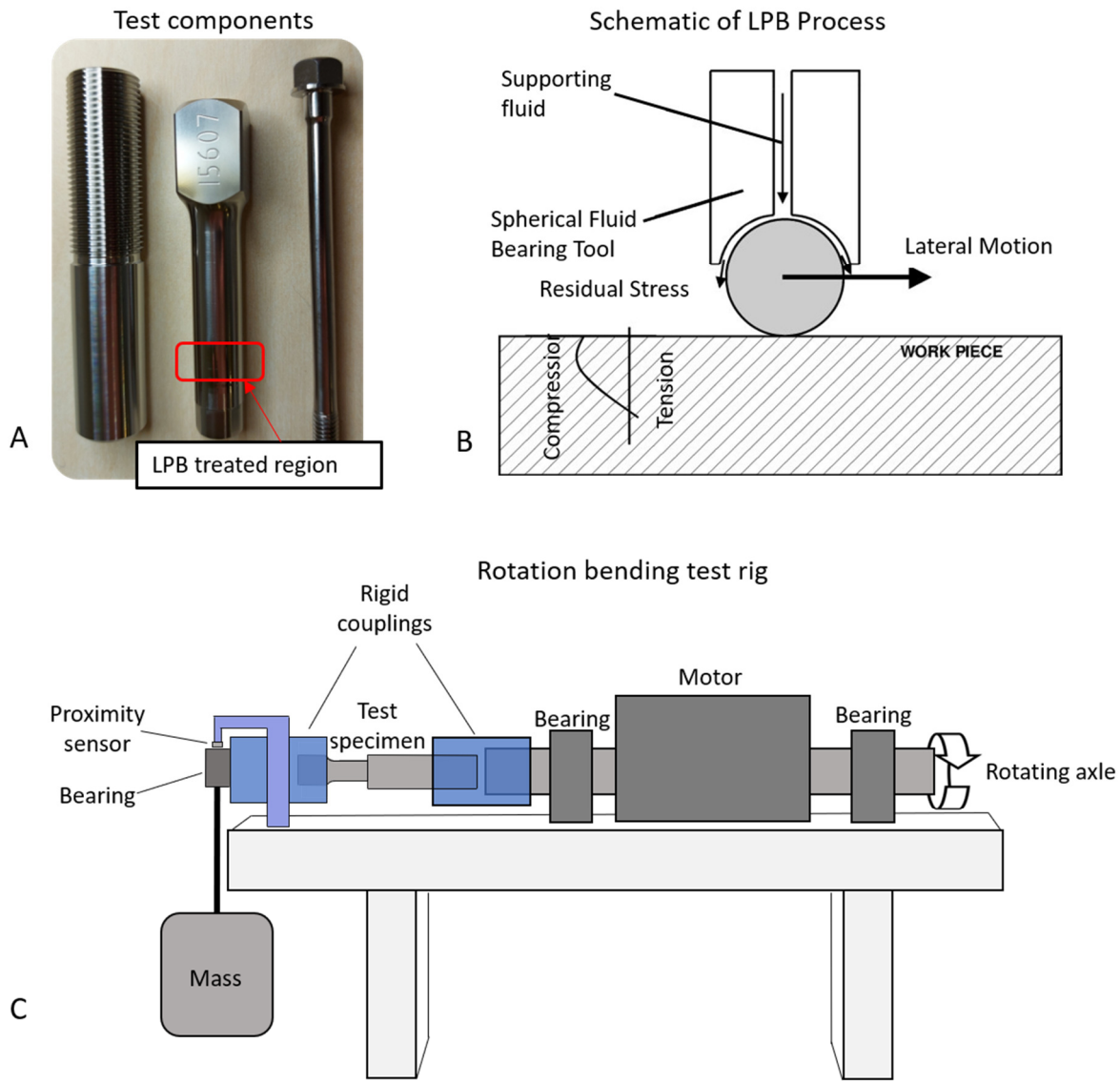

Figure 11. The figure is from [100] *(Paper V) and shows the following: (A) Tested components, (B) A schematic illustration of the LPB process (adapted with permission from Prevéy and Telesman 2000* [101]*), (C) A schematic illustration of the rotation bending test setup.*

The test components were divided into a Control group and an LPB group of which the abutments in the latter group underwent LPB processing. The test components were assembled into test specimens before undergoing rotation bending fatigue tests. Following the tests an analysis of the contacting surfaces was conducted using optical microscopy, scanning electron microscopy (SEM) and interference profilometry. The results from the rotation bending tests are shown in Figure 12.

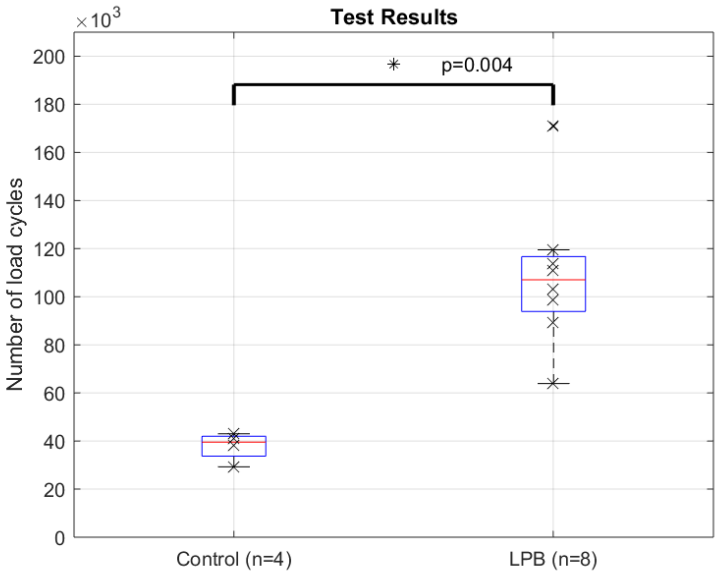

Figure 12. Boxplot showing the number of load cycles in the rotation bending tests [100] *(Paper V). Each test is denoted with a black "x". The median is denoted with a horizontal red line.*

6.1.1. Conclusions from Paper V

- Rotation bending fatigue tests performed on LPB treated and untreated test specimens demonstrate that the LPB treatment leads to statistically significantly increased resistance to fretting fatigue (LPB treated test specimens withstood on average 108 780 load cycles as compared with 37 845 load cycles for untreated test specimens, p = 0.004).

- LPB treated test specimens exhibited less wear at the modular interface as compared with untreated test specimens.

- The LPB surface treatment may lead to reduced risk of fretting induced component failure with the consequence of a reduced need for implant revisions.

7. Preparation for clinical implantation

Within the scope of the thesis, the first steps towards clinical implantation have been taken. A research protocol has been developed for assessing the ability of the neuromusculoskeletal interface to facilitate bidirectional communication between muscles and nerves within the residual limb and the external prosthesis. Specifically, it will be assessed whether myoelectric activity recorded via the neuromusculoskeletal interface can be used to control a lower limb prosthesis and whether sensations perceived in the missing limb can be elicited to provide sensory feedback from the prosthesis. The research study will also assess whether the neuromusculoskeletal interface may lead to functional improvements in individuals with lower limb amputation. Risk analyses have been performed to minimize the risks not only with the surgical aspects, and clinical use of the neuromusculoskeletal interface, but also on the research activities to be performed within the clinical investigation. The neuromusculoskeletal interface has never been used in the lower limb or in combination with active lower limb prosthetic components. Furthermore, compared with research and testing of upper limb prostheses, research and testing of lower limb prostheses is inherently more hazardous due to the risk of falling and subsequent injuries [102]. To address this, a stepwise safety protocol has been developed for the research scenarios involving the recipient(s) of the neuromusculoskeletal interface within the clinical investigation [103] (Paper VI).

7.1. Stepwise safety protocol for lower limb prosthetic risk management in a clinical investigation – Paper VI

The safety protocol was developed to evaluate neuromusculoskeletal prostheses for the lower limb but it can be applied to any new leg prostheses and control strategies. To minimize the risks for the research participants, a number of safety levels have been defined (Figure 13). Every time a new or modified prosthesis is to be implemented with a research participant, the stepwise safety protocol must be followed, starting from the highest safety level. Each safety level has at least one test method with required outcome(s) that must be met before advancing to the next lower level (or sub-level). Specific precautions during ambulation, including walking aids, and type of environment are defined per each level.

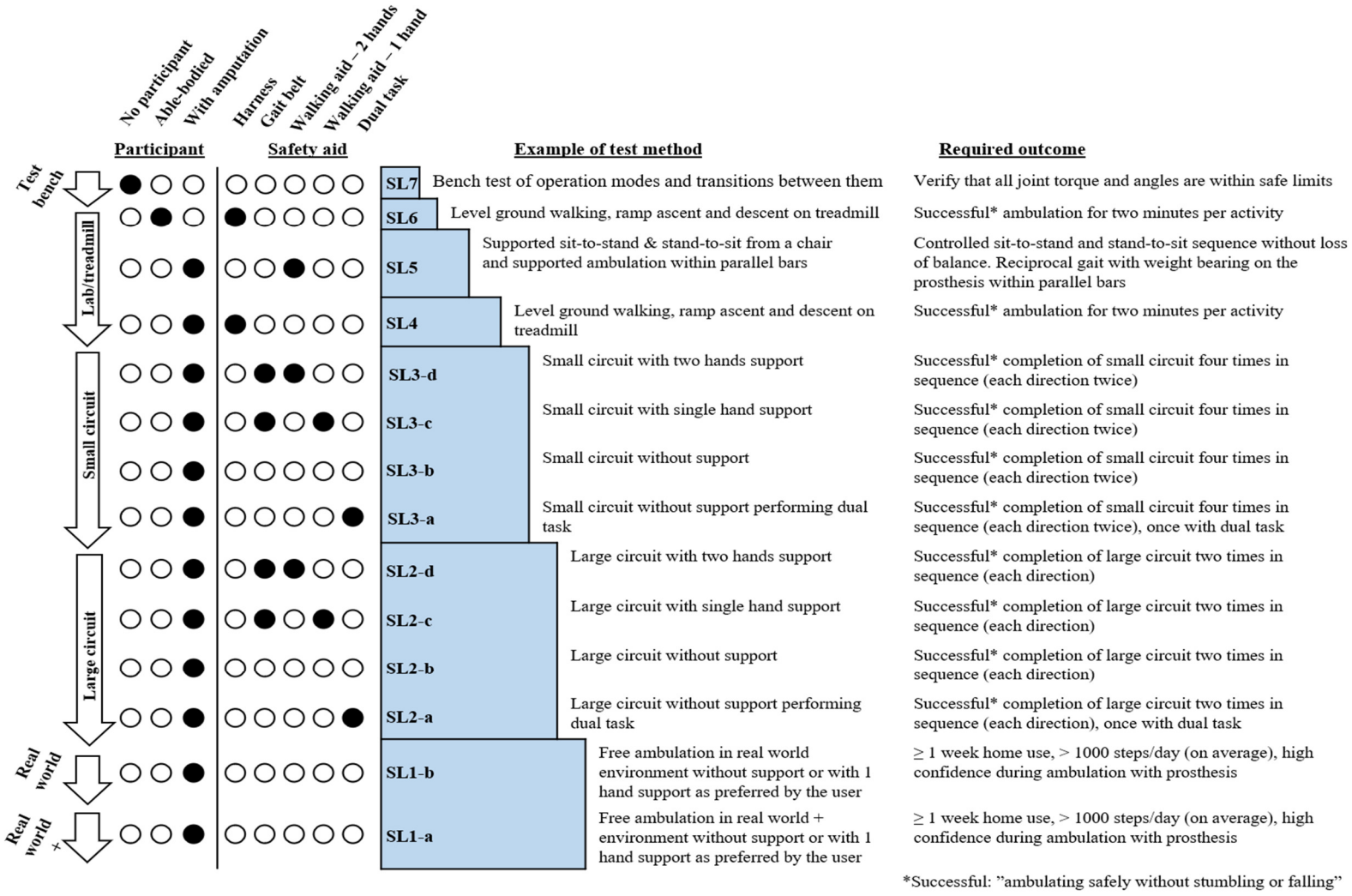

Figure 13. The figure is from [103] *(Paper VI) and shows the stepwise safety protocol. From left to right the columns denote: (1) Test environment applicable for each safety level, (2) Type of participant applicable for each safety level, (3) Type of safety aid to be used and whether dual tasks are to be performed, at each safety level. (4) Stepwise safety levels, (5) Examples of test methods to be performed at each safety level, (6) Required outcome to be achieved before progression to the next lower safety level is allowed. The safety protocol is described in more detail in* [103] *(Paper VI).*

8. Summary of thesis contributions

Within the scope of this thesis, a new design of the neuromusculoskeletal interface for neural control and sensory feedback of bone-anchored lower limb prostheses has been developed. The new design has an improved structural capacity compared with current OPRA Implant System and facilitates the translation of the e-OPRA technology to amputations of the lower limb. Furthermore, the first steps towards clinical implantation of the system within a clinical investigation have been taken by development of a clinical research protocol that has been approved by the Swedish Ethical Review Authority. Contributions from individual papers are summarized below.

Paper I

Paper I provided a review of literature on implant systems for bone-anchored attachment of limb prostheses. The review was focused on the mechanical features of the implant systems, their interfaces with surrounding biological tissue, and their design characteristics, in contrast to other published reviews which have been more focused on reporting functional and clinical outcomes.

Paper II

Paper II presented the largest set of load data for individuals treated with bone-anchored prostheses, regardless of amputation level, implant system, and measurement technique. The load data, measured directly at the bone-anchored implant during daily walking activities, can be used as input for further development of implant system designs, and clinically relevant methods for testing of this type of implant systems. Within this work it was further investigated how the use of walking aids affect the load levels at the bone-anchored interface. This information is crucial for understanding how to reduce the risk of mechanical complications with this type of prosthetic attachment, and it may also guide rehabilitation protocols both for the aggregate population and individually tailored for specific patients.

Paper III

Paper III provided the first evaluation of the anticipated loads at the bone-anchored interface during running. Knowledge of the load characteristics at the bone-implant interface during high-loading activities is scarce. However, this information is needed to understand the limitations of current implant systems, as well as to inform their future development.

Paper IV

In Paper IV Finite Element Analysis was used to investigate the effects of thread profile parameters, cortical thickness, and bone stiffness characteristics for the stress and strains generated in bone-anchored implants and surrounding bone tissue. The study was conducted using a parameterized model of a bone-anchored implant system and surrounding bone to ensure wide applicability of the results and to generate knowledge on how to optimize the design in further developments of these systems.

Paper V

Paper V presented results from an experimental investigation of a surface enhancement method to improve the fretting resistance of bone-anchored implants for attachment of limb prostheses. The results from the study concluded that substantial improvements are achievable which may translate into increased service life, reduced need for component replacements, and increased loadbearing capacity for this and similar applications.

Paper VI

Paper VI presented a stepwise safety protocol for managing the risks when conducting research on active prosthetic legs, with modifiable control systems. The protocol can be applied to any new leg prosthesis or control system for controlling a lower limb prosthesis. It may serve as a reference for safety precautions to consider when conducting research and development of lower limb prostheses.

9. General conclusions and future work

Extensive research has shown the benefits of bone-anchored attachment of lower limb prostheses and the maturity and clinical acceptance of this technology is increasing. Developments in implant system design, surgical procedures and external safety devices have reduced the rate of mechanical failure and infectious complications. The work in this thesis may potentially contribute to a continuation of this trend by further reduction of mechanical complications and reduced restrictions on high loading activities. Previous work has shown that the bone-anchored implant may serve as a mechanically stable human-machine gateway which allows for permanent use of implanted electrodes with percutaneous leads and that this may be used to provide intuitive prosthesis control and sensory feedback for individuals with upper limb amputation. The translation of this technology to lower limb amputations is currently underway, aided by the development of the neuromusculoskeletal interface within this thesis. It is hypothesized that this technology will allow for intuitive prosthesis control, sensory feedback, and functional improvements also for individuals with lower limb amputation. The neuromusculoskeletal interface provides a unique platform for harnessing the underexploited control information of muscles and nerves in the residual limb. A number of promising surgical techniques have been developed in recent years by which the amputated limb is surgically modified to increase the capacity for extraction of control information. TMR, RPNI and AMI are all very well suited for use in combination with the neuromusculoskeletal interface.

However, before this can be explored, verification testing of the developed neuromusculoskeletal interface must be completed to ensure safety and adherence to regulatory requirements. The efficacy of the neuromusculoskeletal interface should then be assessed in controlled research studies within a clinical investigation.

The function of the neuromusculoskeletal interface is limited to providing direct connection between the skeleton, nerves and muscles and the external prostheses. Thus, results in outcome measures evaluating prosthetic function for the user are not exclusively determined by the performance of the neuromusculoskeletal interface. The functional outcome will also be affected by clinical aspects such as the pre-surgery condition, anatomy, surgical outcome and rehabilitation. The functional outcome will also depend on the algorithms used for controlling the prosthesis, the prosthetic hardware to facilitate the intended movements and the ability to provide adequate sensory feedback. A clinical investigation must consider all these aspects and be carefully planned to minimize the risk for the research participants while objectively exploring the new opportunities for lower limb prosthesis control. The ultimate aims are to improve the quality of life for the users, to reduce the disability of the amputation and to pave the way for clinical translation.

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